

ON THE CONFIGURATION AND THE CONFORMATION OF 2-ACYLINDAZOLE
ARYLHYDRAZONES

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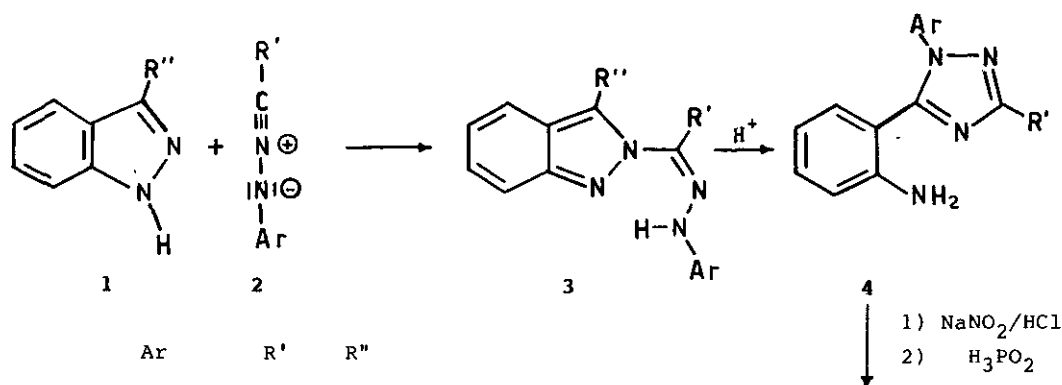
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Abstract — The Z configuration of 2-acylindazole arylhydrazones 3 was assigned on the basis of solvent effects on their ¹H-nmr spectra. Due to free rotation around the N-C bond, the title compounds exist in a solvent dependent equilibrium between the intramolecular N-H bonded conformer 6 and its rotamers.

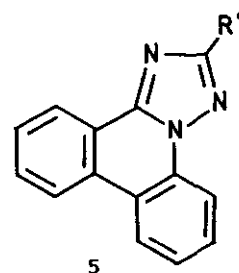
In a previous paper, we described the 1,3-addition reaction of indazole 1 with nitrilimines 2a, 2b and 2d to give 2-acylindazole phenylhydrazones 3, and the further transformation of hydrazones 3 into 1-phenyl-5-(*o*-aminophenyl)-1,2,4-triazole derivatives 4 and into 1,2,4-triazolo[1,5-*f*]phenanthridines 5.¹ The hydrazone structure of compounds 3a, 3b and 3d had been confirmed by analytical and spectral data as well as by the structures of products 4 and 5 obtained.

However, since the Z configuration of hydrazones 3 plays an important role in the postulated acid catalysed rearrangement of 3 to give 4¹, an investigation of the structure of intermediates 3, involving ¹H-nmr spectroscopy and infrared spectroscopy was warranted.

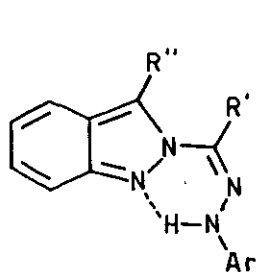
For the purpose of this study, additional hydrazones 3c and 3e-h were prepared following the established procedure.¹ The ¹H-nmr data in CDCl₃ confirm the 2-substituted indazole structure for 3a-h: H-4 and H-7 are distinct and display the expected chemical shifts, for 3b-g H-3 was found downfield from H-3 for the parent compound indazole and the characteristic ⁵J_{H3-H7} was determined to be ca 1 Hz in all cases, as required² (see Experimental).



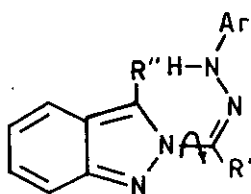
	Ar	R'	R''
a	Ph	Ph	H
b	Ph	CO ₂ Et	H
c	Ph	CO ₂ Me	H
d	Ph	COMe	H
e	4-Cl-C ₆ H ₄	COMe	H
f	4-Me-C ₆ H ₄	COMe	H
g	4-MeO-C ₆ H ₄	COMe	H
h	Ph	COMe	Me



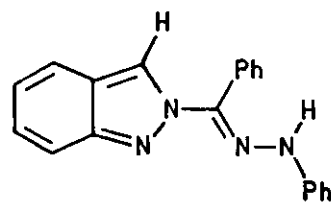
The following tautomeric structures are conceivable for adducts 3 : hydrazones 6-8 and the diazo tautomer 9, for 3b-h also the enolic tautomer 10.



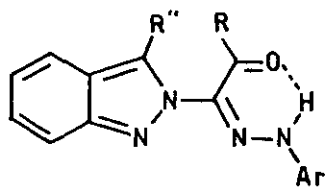
6 (Z N-H bonded)



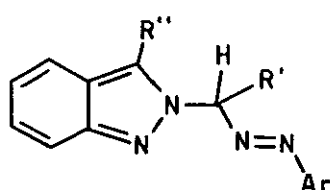
7 (Z N-H free)



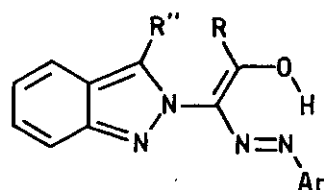
8a (E)



8b-h (E)



9



10

Structure 9 is immediately ruled out by the presence of a low field signal in the ^1H -nmr spectrum (N-H or O-H), while infrared data exclude the enolic structure 10.³ Carbonyl stretching frequencies in CHCl_3 at ca 1710 cm^{-1} (3b,c) and ca 1680 cm^{-1} (3d-h) (see Table) represent conjugated, non-hydrogen bonded ester and ketone carbonyl absorptions, respectively. This also presents first evidence against structure 8, in which the E - configuration of the hydrazone should, in the case of 3b-h, lead to a strong intramolecular N-H---O hydrogen bond.⁴

The ^1H -nmr chemical shift values for the N-H and H-3 protons for hydrazones 3a-h in solvents of increasing polarity (benzene, chloroform, acetone, dimethyl sulfoxide) are given in the Table.

Table : Chemical Shift Values for N-H and H-3 Protons and Carbonyl Stretching Frequencies for Hydrazones 3a-h

	Ar	R'	R''	δ N-H				δ H-3				ν C=O cm^{-1}
				C_6D_6	CDCl_3	$\text{C}_3\text{D}_6\text{O}$	DMSO	C_6D_6	CDCl_3	$\text{C}_3\text{D}_6\text{O}$	DMSO	
3a	Ph	Ph	H	11.17	10.65	10.37	10.01	7.30	8.09	8.44	8.68	--
3b	Ph	CO_2Et	H	13.07	12.66	12.07	11.02	8.84	8.86	8.84	8.70	1710
3c	Ph	CO_2Me	H	13.09	12.73	12.08	11.04	8.79	8.88	8.84	8.70	1712
3d	Ph	COMe	H	13.36	13.08	12.54	11.36	9.09	8.99	8.87	8.61	1680
3e	4-Cl- C_6H_4	COMe	H	13.24	13.18	12.61	11.36	9.08	9.00	8.87	8.60	1680
3f	4-Me- C_6H_4	COMe	H	13.39	13.02	12.52	11.33	9.11	8.98	8.87	8.60	1680
3g	4-MeO- C_6H_4	COMe	H	13.37	13.03	12.49	11.28	9.16	8.98	8.86	8.59	1675
3h	Ph	COMe	Me	10.58	9.96	10.41	10.76	--	--	--	--	1680

Figure 1 shows the dependence of the chemical shift values of the N-H protons of compounds 3a-h upon the solvent used. For compounds 3a-g a marked upfield shift is observed in the series benzene - dimethyl sulfoxide, characteristic for the presence of an intramolecular hydrogen bond⁵ (structure 6). For the 3-methyl derivative 3h, the bulky substituent in the 3-position does not permit the near coplanar arrangement required by conformer 6 and thus does not allow the formation of a strong intramolecular hydrogen bond. This was confirmed by the chemical shift value for the N-H resonance of 3h being concentration dependent while this was not the case for derivatives 3a-g (see Experimental). Evidently, if configuration 8 were correct, a 3-substituent should not affect the then present N-H---O hydrogen bond (as in structure 8b-h). Furthermore, the chemical

shift values for the N-H resonance for compound 3a follow the general pattern, in the absence of either ester or ketone functionality.

Figure 2 depicts the dependence of the chemical shift values for protons H-3 upon the solvent used. Again, for compounds 3b-g an intramolecular hydrogen bond is indicated, as present in structure 6, where H-3 protons experience the deshielding effect of the coplanar carbonyl group. For the phenyl derivative 3a an at first sight surprising pattern is observed.

FIGURE 1

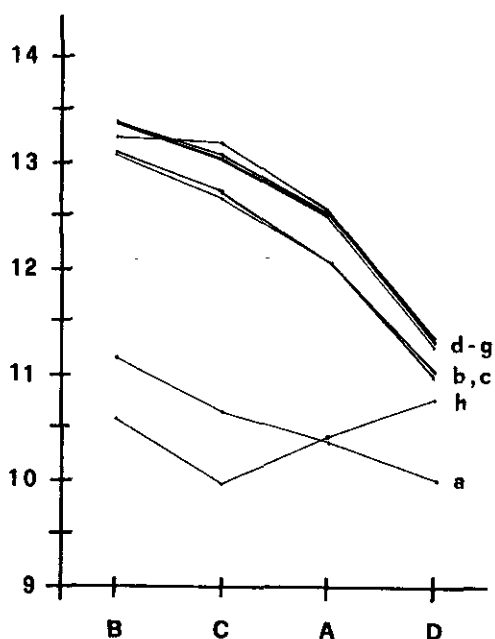
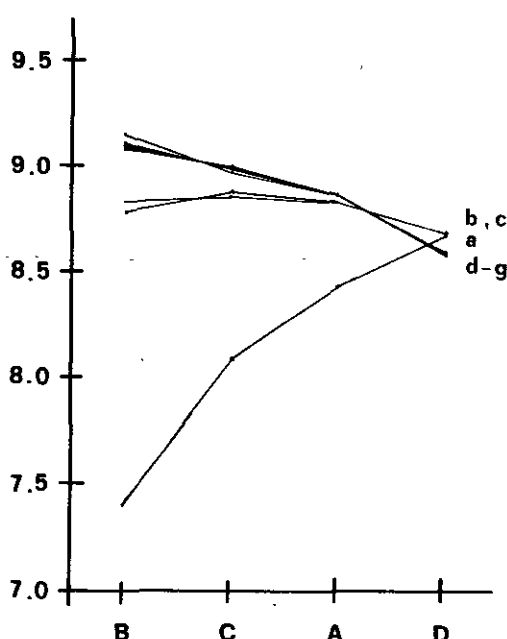


FIGURE 2



Figures 1 + 2: Graph of chemical shift values as a function of the solvent : Benzene (B), Chloroform (C), Acetone (A), Dimethyl sulfoxide (D).
Figure 1 : N-H resonances. Figure 2 : H-3 resonances.

In nonpolar solvents, with the predominant conformer being 6, H-3 is ideally located within the shielding cone of the benzene ring, which, sterically, will be forced into a position perpendicular to the plane of the molecule. With increasing solvent polarity, the intramolecular N-H---N hydrogen bond is broken and the coplanarity is destroyed, leading to a downfield shift of the H-3 resonance also as a function of the interaction between H-3 and the solvent.² Electronwithdrawing and electrondonating substituents on the phenylhydrazone moiety (3d-g) proved to have only a minor effect on the strength of the hydrogen bond.

The observed solvent effects can be well interpreted considering the hydrazones **3a-g** existing as their Z - isomers. Due to free rotation around the N-C bond, the hydrazones exist in a solvent dependent equilibrium between the intramolecular N-H bonded rotamer **6** and the N-H free **7**, whereby the N-H and the H-3 chemical shift values represent a weighted time average for the rapid exchange between **6** and its rotamers.

EXPERIMENTAL

Melting points were determined with a Kofler hot-stage apparatus; ir spectra were recorded on a Perkin-Elmer infrared spectrometer (model 297), solutions being prepared by dissolving 0.03 mmol of the corresponding hydrazone in 1 ml of chloroform; uv spectra (ethanol) were determined with a Varian Superscan 3 spectrophotometer; ^1H -nmr spectra were recorded on a Varian XL 200 FT NMR spectrometer (operating at 200.057 MHz; TMS as internal standard), acquisition time 3,072 s, spectral window 3000.3 Hz, number of points 18,432, pulse width 4s, solutions being prepared by dissolving 0.03 mmol of the corresponding hydrazone in 1 ml of benzene- d_6 , chloroform- d , acetone- d_6 or dimethyl sulfoxide- d_6 .

General Method for the Preparation of the 2-Acylindazole Arylhydrazones 3.

Compounds **3** were prepared according to the procedure described previously¹ for **3a,b,d**, by treatment of **1** with equimolar amounts of suitable hydrazidoyl chloride^{1,6} and threefold excess of triethylamine in anhydrous THF, and were crystalized from ethanol.

Compound 3a (Ar = Ph, R' = Ph, R'' = H) (yield 50%), mp 104°C; ^1H -nmr (CDCl_3) δ : 6.91-7.42 (m, 10H, ArH), 7.62 (m, 2H, ArH), 7.71 and 7.86 (2m, 2H, H-4 and H-7), 8.09 (d, 1H, H-3, $^5J=1.9$ Hz), 10.65 (s, 1H, NH); uv nm λ_{max} (log ϵ): 232sh(4.38), 296(4.20), 350(4.29).

Compound 3b (Ar = Ph, R' = CO_2Et , R'' = H) (yield 77%), mp 128°C; ^1H -nmr (CDCl_3) δ : 1.47 (t, 3H, OCH_2CH_3), 4.45 (q, 2H, OCH_2CH_3), 7.04-7.35 (m, 7H, ArH), 7.72-7.77 (m, 2H, H-4 and H-7), 8.86 (d, 1H, H-3, $^5J=0.9$ Hz), 12.66 (s, 1H, NH); uv nm λ_{max} (log ϵ): 229(4.21), 286(4.10), 356(4.32).

Compound 3c (Ar = Ph, R' = CO₂Me, R'' = H) (yield 90%), mp 142°C; ¹H-nmr (CDCl₃) δ : 3.99 (s, 3H, OCH₃), 7.05-7.41 (m, 7H, ArH), 7.73-7.76 (m, 2H, H-4 and H-7), 8.88 (d, 1H, H-3, ⁵J=1.9 Hz), 12.73 (s, 1H, NH); uv nm λ_{max} (log ε) : 230(4.21), 285(4.11), 357(4.34). Anal. Calcd. for C₁₆H₁₄N₄O₂ : C, 65.29; H, 4.80; N, 19.04. Found : C, 65.35; H, 4.82; N, 18.95.

Compound 3d (Ar = Ph, R' = COMe, R'' = H) (yield 93%), mp 140°C; ¹H-nmr (CDCl₃) δ : 2.72 (s, 3H, COCH₃), 7.07-7.36 (m, 7H, ArH), 7.71-7.75 (m, 2H, H-4 and H-7), 8.99 (d, 1H, H-3, ⁵J=0.9 Hz), 13.08 (s, 1H, NH); uv nm λ_{max} (log ε) : 234(4.16), 291(4.10), 367(4.36).

Compound 3e (Ar = 4-Cl-C₆H₄, R' = COMe, R'' = H) (yield 80%), mp 178°C; ¹H-nmr (CDCl₃) δ : 2.71 (s, 3H, COCH₃), 7.10-7.32 (m, 6H, ArH), 7.68-7.77 (m, 2H, H-4 and H-7), 9.00 (d, 1H, H-3, ⁵J=0.9 Hz), 13.18 (s, 1H, NH); uv nm λ_{max} (log ε) : 236(4.18), 291(4.17), 368(4.41). Anal. Calcd. for C₁₆H₁₃N₄OCl : C, 61.44; H, 4.19; N, 17.91. Found : C, 61.55; H, 4.21; N, 17.86.

Compound 3f (Ar = 4-Me-C₆H₄, R' = COMe, R'' = H) (yield 92%), mp 175°C; ¹H-nmr (CDCl₃) δ : 2.35 (s, 3H, CH₃), 2.70 (s, 3H, COCH₃), 7.09-7.38 (m, 6H, ArH), 7.73-7.77 (m, 2H, H-4 and H-7), 8.98 (d, 1H, H-3, ⁵J=1.0 Hz), 13.02 (s, 1H, NH); uv nm λ_{max} (log ε) : 236(4.16), 291(4.12), 373(4.40). Anal. Calcd. for C₁₇H₁₆N₄O : C, 69.84; H, 5.52; N, 19.17. Found : C, 70.00; H, 5.53; N, 19.24.

Compound 3g (Ar = 4-MeO-C₆H₄, R' = COMe, R'' = H) (yield 70%), mp 134°C; ¹H-nmr (CDCl₃) δ : 2.69 (s, 3H, COCH₃), 3.82 (s, 3H, OCH₃), 6.92-7.41 (m, 6H, ArH), 7.69-7.76 (m, 2H, H-4 and H-7), 8.98 (d, 1H, H-3, ⁵J=0.9 Hz), 13.03 (s, 1H, NH); uv nm λ_{max} (log ε) : 234(4.14), 296(4.12), 383(4.35). Anal. Calcd. for C₁₇H₁₆N₄O₂ : C, 66.22; H, 5.23; N, 18.17. Found : C, 66.41; H, 5.19; N, 18.25.

Compound 3h (Ar = Ph, R' = COMe, R'' = Me) (yield 72%), mp 188°C; ¹H-nmr (CDCl₃) δ : 2.52 (s, 3H, CH₃), 2.69 (s, 3H, COCH₃), 7.03-7.40 (m, 7H, ArH), 7.64-7.68 (m, 2H, H-4 and H-7), 9.96 (s, 1H, NH); (CDCl₃ ca 1 mg / 0.5 ml) δ : 9.93 (s, 1H, NH); uv nm λ_{max} (log ε) : 232sh(4.18), 285sh(4.00), 345(4.36). Anal. Calcd. for C₁₇H₁₆N₄O : C, 69.84; H, 5.52; N, 19.17. Found : C, 69.97; H, 5.53; N, 19.14.

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